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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,008	09/22/2003	Claude Michel Wischik	WISC3004/JDB	5847

23364 7590 12/27/2006  
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ALEXANDRIA, VA 22314

EXAMINER
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SAMALA, JAGADISHWAR RAO

ART UNIT	PAPER NUMBER
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1618

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/27/2006	PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

# Office Action Summary

Application No.

10/665,008

Applicant(s)

WISCHIK ET AL.

Examiner

Jagadishwar R. Samala

Art Unit

1618

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 175-210 is/are pending in the application.
- 4a) Of the above claim(s) 180-189 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 175-179 and 200-210 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>See Continuation Sheet</u> . | 6) <input type="checkbox"/> Other: ____.  |

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :09/22/06,  
10/31/06 and 11/08006.

## DETAILED ACTION

### Status of Application

Receipt of the response to Restriction requirement and Applicant's arguments/remarks filed on 11/14/2006 is acknowledged.

Election was made **without traverse** and election is made **Final**. Applicant's election of species/ligand "methylene blue" is acknowledged. Claims 175-210 are pending. Claims 175-179 and 200-210 are examined. Non elected claims 180-189 are withdrawn from consideration.

Claims 175-179 and 200-210 are rejected.

### Claim Objection

Claim 202 is objected to because of the following informalities: Claims should not include Figures. Appropriate correction is required. See MPEP § 2173.05(s).

### *Claim Rejections - 35 USC § 112*

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 207 is rejected under 35 U.S.C. 112, first paragraph, because the specifications does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope wherein the blocking ligand consisting of labeled FDDNP: a benzothiazole core

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structure bearing various substituents in the instant claim. In the instantly claimed blocking ligand, the mode of attachment or linkage of one of the phenylene substituent to the benzene ring carrying the NR<sub>2</sub> group is not clearly understood. Given its broadest reasonable interpretation, any blocking ligand consisting of [18F] FDDNP; a benzothiazole core structure, even synthesized are troublesome or extremely very tedious process. To this end, given that the instant invention is drawn to a method for determining the stage of neurofibrillary degeneration associated with Alzheimer's Disease, the examiner respectfully submits that one of ordinary skill in the art would be faced with an undue experimental burden in attempting to practice the invention commensurate in scope with the claim. That is, the instant invention is concerned with a wide range of blocking ligands, such as the ones set forth in the instant claim and specification, and an ordinary practitioner would need to undergo undue experimentation in order to develop an effective method of enhancing for the detection of blocking ligand capable of modulating or inhibiting pathological tau-tau protein association and pathological neurofilament aggregation and particularly useful in screening substances for the prophylaxis and treatment of Alzheimer's Disease without guidance from the prior art. As such, this disclosure of the instant specification is not sufficient to support the recitation of the instant claim.

***Claim Rejections - 35 USC § 102***

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. Claims 175-179 are rejected under 35 U.S.C. 102(b) as being anticipated by Wischik et al. (WO 96/30766).

Claims 175-179 are drawn to a method for determining the stage of neurofibrillary degeneration associated with a tauopathy in a subject believed to suffer from the Alzheimer's Disease (using ligand e.g. methylene blue capable of labeling aggregated paired helical filament PHF tau protein).

Wischik discloses method for the detection of substances capable of modulating or inhibiting pathological tau-tau protein association and pathological neurofilament aggregation and particularly useful in screening substances for the prophylaxis and treatment of Alzheimer's Disease (see abstract). Wischik also discloses the use of phenothiazine compounds and pharmaceutically acceptable salts thereof in the manufacture of a composition for the prophylaxis and treatment of pathological tau-tau or pathological neurofilament aggregation, and especially for the prophylaxis and treatment of Alzheimer's Disease. Wischik further discloses that phenothiazine (methylene blue) compounds can be used in the treatment or prophylaxis of Alzheimer's disease, particularly for the blocking, modulating and inhibiting of pathological tau-tau association (see page 30, lines 33 and page 31, lines 1-2). Therefore, all critical elements as required by instant claims are taught by the cited reference and claims are anticipated.

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 175-179 and 200-210 are rejected under 35 U.S.C. 103(a) as being unpatentable over Peter Friedhoff et al. (Biochemistry 1998, 37, 10223-10230 here after Peter) view of Wischik et al (Proc. Natl. Acad. Sci 1996, 93, 11213-11218 here after Wischik) and Quay et al. (US 5,008,099 here after '099)

Peter discloses the method of using the thioflavin S or T derivatives, in the diagnosis, which can be used to stain amyloid-like deposits and neurofibrillary tangles in postmortem brains and can be used to quantify the formation of paired helical filaments from tau protein (see page 10223).

Peter fails to disclose the use of Methylene blue compounds as ligands that binds to tau protein. However, the use of Methylene blue compound a ligand capable of labeling aggregating paired helical filament (PHF) tau protein is well known in the art as shown by Wischik.

Wischik discloses a method for detecting Alzheimer's disease by selectively using phenothiazine (methylene blue) compounds to facilitate the proteolytic degradation of tau aggregates and prevent the further propagation of tau capture in Alzheimer's disease (see abstract).

It would have been obvious to one of ordinary skill in the art to modify the thioflavin derivatives disclosed by Peter as blocking ligand in combination with methylene blue compound capable of labeling aggregating paired helical filament (PHF) tau protein because Wischik teaches that, methylene blue, a histological marker for amyloid, showed reverses the proteolytic stability of protease-resistant PHFs by blocking the tau-tau binding interaction through the repeat domain. Additionally methylene blue at higher concentrations, reverses the proteolytic stability of the core tau fragment within PHFs by preventing the tau-tau binding interactions needed to maintain the structure of the PHF core. One of ordinary skill in the art would have been motivated to include the methylene blue derivatives as a ligand that binds to an tau protein by contacting neurofibril tissue effectively compared to a normal control level of binding disclosed by Peter because the methylene blue, a histological marker for amyloid protein taught by Wischik, while having a similar effect as a detectably-labeled compound that binds to an tau protein, provides an additional and separate advantage as compared to the binding agent disclosed by Peter.

As evident from '099 patent wherein method of determining the presence and location of amyloid deposits in an organ or area of a patient is achieved by intravenous administration of an imaging effective compounds such as benzothiazolesulfonic acid derivatives. As recited in claims 207-210 wherein the blocking ligand is a thioflavin-T having the same core structure, the imaging compounds used for detection of amyloid deposits by '099 inherently will have similar function of binding ligand which labels the competing binding sites present in the relevant region of the brain of a patient.

**Conclusion**

1. At present no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jagadishwar R. Samala whose telephone number is (571)272-9927. The examiner can normally be reached on 8.30 A.M. to 5.00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571)272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

**VICKIE KIM**  
**PRIMARY EXAMINER**

Jagadishwar R Samala  
Examiner  
Art Unit 1618

sjr